ORIGINAL ARTICLE

# Efficacy of 5-day cefpodoxime proxetil for recurrent pharyngitis in adults. A comparative study with 10-day penicillin V or amoxycillin–clavulanate

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**Objective:** To compare the clinical and bacteriologic efficacy of a 5-day course of cefpodoxime proxetil (CPD) with that of a 10-day course of penicillin V (PNV) or amoxycillin–clavulanate (AMC) in recurrent pharyngitis in adults. A cost-effectiveness study (reported elsewhere) was carried out at the same time.

**Methods:** This multicenter, randomized, open label trial involved 580 adult patients consulting general practitioners for clinical recurrent pharyngitis (≥3 episodes within the last 12 months) regardless of the bacterial etiology. Patients were treated for 5 days with CPD, 100 mg twice daily, or for 10 days with PNV, $1 \times 10^6$ IU three times a day, or for 10 days with AMC, 500 mg (amoxycillin) three times a day. Clinical and bacteriologic outcomes were noted at the end of treatment, and cases of clinical recurrence were recorded during a 6-month follow-up period.

**Results:** At the end of treatment, clinical response was satisfactory in 157 of 170 (92.3%) patients on CPD, 147 of 166 (88.5%) patients on PNV, and 168 of 177 (94.9%) patients on AMC. Group A β-hemolytic streptococci (GABHS) were eradicated in 22 of 23 (95.65%) patients on CPD, 16 of 16 (100%) patients on PNV, and 19 of 20 (95%) patients on AMC. The rates of clinical success and GABHS eradication were not significantly different between the groups. Compliance ($p<0.001$) and tolerance ($p<0.001$) were significantly better in the CPD group than in the other two groups. Among the 389 patients evaluable 6 months after the end of treatment, the recurrence rate of acute pharyngitis (due to any bacterium) was significantly lower in the CPD group ($p=0.01$ versus PNV; $p<0.01$ versus AMC). A Kaplan–Meier analysis (469 patients over 6 months) of the rate of non-recurrence, with comparison by the log-rank test, also showed a significant difference in favor of CPD.

**Conclusions:** A 5-day treatment of recurrent pharyngitis with CPD was as effective and better tolerated than a 10-day treatment with PNV or AMC. The risk of recurrence was lower with CPD.

**Key words:** Recurrent pharyngitis, short-course therapy, cefpodoxime proxetil, penicillin V, amoxycillin–clavulanate

## INTRODUCTION

The diagnosis of acute pharyngitis is generally based on clinical signs and symptoms. In most cases, antibiotic treatment is dictated by the risk of suppurative complications and, above all, by the risk of failing to abrogate pharyngitis due to group A β-hemolytic streptococci (GABHS). GABHS pharyngitis represents 11–50% of cases of acute pharyngitis, and the risk of acute rheumatic fever (ARF) after GABHS pharyngitis is 1 to 3% in the absence of antimicrobial chemotherapy [1].

In France, clinicians are advised to treat all cases of acute pharyngitis, regardless of the age of the patient, and without taking a throat swab for identification of

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group A streptococci [1]. A 10-day course of penicillin V (PNV) remains the reference treatment of these acute episodes. This therapeutic strategy differs from that applied in cases of recurrent pharyngitis, where β-lactam agents stable to β-lactamases (second- and third-generation cephalosporins, aminopenicillins combined with a β-lactamase inhibitor) are the recommended treatment.

In the literature, the yearly frequency of episodes is used as a practical definition of recurrent pharyngitis. Depending on the author, recurrent episodes (from three to five) can be counted over a 2-year or 1-year period [2–10].

The pathophysiologic mechanisms and bacterial epidemiology of these episodes of recurrent pharyngitis remain to be documented. Potentially predisposing factors include bacterial colonization of hypertrophic tonsils (2,6,10–12) and the copathogenicity hypothesis [13]. The latter is based on the presence of large numbers of β-lactamase-producing strains in the tonsils of patients with recurrent pharyngitis. Among the β-lactam agents used to treat episodes of pharyngitis, PNV and aminopenicillins are sensitive to many β-lactamases, and this may possibly explain cases of treatment failure and recurrence.

Cefpodoxime proxetil (CPD), a cefpodoxime prodrug, is a β-lactam agent and an oral third-generation cephalosporin. In France, as far as the treatment of pharyngitis is concerned, CPD should be reserved for the treatment of recurrent episodes. Several comparative trials of CPD in the treatment of streptococcal pharyngitis have shown that this antibiotic is a safe and effective alternative for the eradication of group A streptococci [14–16]. In addition, a 5-day course of cefpodoxime in this setting is as effective in clinical and bacteriologic terms (eradication of group A streptococci) as a 10-day course of PNV [15,17–20], with a clear benefit as regards compliance.

These observations led us to perform a clinical study on adult patients with recurrent pharyngitis to compare a 5-day course of CPD with a 10-day course of PNV or amoxycillin–clavulanate (AMC). The aims of this study were:

1. to compare the clinical efficacy at the end of treatment;
2. to compare the bacteriologic efficacy in the subgroup of documented GABHS pharyngitis;
3. to compare the clinical efficacy on the recurrence rate during the 6-month follow-up period.

Results of the cost-effectiveness study conducted in parallel have been published elsewhere [21].

## PATIENTS AND METHODS

This French nationwide multicenter study, conducted from March 1992 to January 1993, involved 580 patients recruited by 204 general practitioners. Each investigator had to include at least a block of three patients, who were randomly assigned to one of the three regimens under study. It was thus a prospective, comparative, randomized, open trial with three parallel groups.

### Patients

Inclusion criteria were as follows: ambulatory patients over 15 years of age, of either sex, consulting a general practitioner for recurrent pharyngitis. The latter was defined by the presence of clinical signs and symptoms of bacterial pharyngitis origin (temperature ≥38 °C, throat pain both spontaneously and on swallowing, possible headache, erythematous or erythemato-exudative tonsils and pharynx, anterior cervical adenopathy; no coryza, conjunctivitis, cough or laryngitis) and by the frequency of episodes (the current episode having to be at least the third in the last 12 months).

Non-inclusion criteria were as follows: age less than 15 years; pregnancy or breast-feeding; sinusitis; history of allergy to β-lactam agents; cancer, hematologic disorder or acquired immunodepression; antibiotic treatment in the previous 72 h; treatment with allopurinol; recurrent infectious lung, urinary tract or gynecologic disease; unlikely compliance with 6 months of follow-up.

All the patients (or the parents of patients less than 18 years old) gave their informed consent to the study and the protocol was approved by a medical ethical committee.

### Treatment regimens

The patients were randomized to one of the following oral treatment arms: CPD, one tablet (100 mg) twice daily for 5 days; PNV, one tablet ($1 \times 10^6$ IU; 600 mg) three times a day for 10 days; AMC, one tablet (500 mg amoxycillin + 125 mg clavulanate) three times a day for 10 days. The tablets had to be taken with meals in the morning and evening (CPD), or morning, midday and evening (PNV and AMC). Treatment allocation was managed via a central computer system. Concomitant administration of antiseptics, analgesics, antipyretics and anti-inflammatory drugs (including steroids) was authorized. In contrast, other antibiotics, even in the form of mouthwashes, were forbidden.

### Clinical follow-up

At the enrollment visit (D1), after checking of inclusion and non-inclusion criteria, the patients' demographic

data and personal histories were recorded, together with details of the current episode of pharyngitis. General and local signs (temperature, loss of appetite, throat pain, headache, color of the pharynx, adenopathy) were noted, together with the allocated treatment, other prescribed drugs and sick leave. The patient was seen by the same investigator at an end-of-treatment visit (D7–D8 in the CPD group; D12–D13 in the PNV and AMC groups) to assess changes in local and general signs, together with compliance, tolerability and how the patient felt. All the patients treated successfully were seen 6 months later. During the follow-up period (from D9 or D14 to D180), the patient was contacted by telephone every 2 months to record any new episodes of pharyngitis or intercurrent infections. When recurrences were diagnosed in the practitioner's office, general and local signs were recorded, along with any drug prescriptions.

#### Bacteriologic follow-up

On D1, the investigator took two swabs in random order, one for diagnosis of group A streptococcal infection by means of a rapid agglutination method (Abbott Test Pack, Abbott, USA), and the other for culture. These two samples allowed an evaluation of the sensitivity of the rapid diagnosis test in routine practice, even though this test is not available in France at the present time. The samples for culture were obtained with Culturette swabs (Becton-Dickinson, USA), which were immediately placed in special transport medium for respiratory tract pathogens (Stuart Transport Medium, UNIPATH, UK) and sent by mail the same day to a central laboratory (Laboratoire du Centre de Diagnostic du Galilée, Torcy Marne-la-Vallée, France). Only those samples received at the laboratory within 3 days after sampling were taken into account to describe the potential pathogens. Description of the potential pathogens was applied to the following selection of bacteria yielded by culture: all group A, C and G β-hemolytic streptococci (irrespective of their quantity); *Haemophilus influenzae* and *Staphylococcus aureus* cultured from samples not containing streptococci; Enterobacteriaceae and non-fermenting Gram-negative bacilli cultured from samples containing none of the above pathogens. Strains of the two last groups of bacteria were taken into account only when present in culture in significant amounts. Culture of a further throat swab was performed at the end of treatment under the same conditions as at the enrollment visit.

#### Assessment of clinical efficacy

At the end of treatment, clinical efficacy was judged satisfactory if the infection was clinically cured or improved. Efficacy was judged unsatisfactory if the infection had deteriorated or if the patient's condition had not improved. It was unevaluable if the study drug had been taken for less than 5 days (or less than 48 h in case of failure) or if inclusion/non-inclusion criteria were not respected. The time (in days) required for the patients to feel better or cured was noted by the investigator on a daily record card filled in by the patient.

At the end of the follow-up period, treatment was judged successful if no further episode of pharyngitis had occurred by D180. Recurrence was defined as the onset of a new episode of pharyngitis after the end-of-treatment visit. Efficacy was unevaluable in the following cases: no follow-up visit or no contact within 6 months after the beginning of treatment; unsatisfactory or unevaluable clinical efficacy at the end-of-treatment visit; prescription of another antibiotic during the follow-up period for an intercurrent infection.

#### Evaluation of efficacy by means of Kaplan–Meier plots

All the patients in whom clinical efficacy was judged satisfactory at the end-of-treatment visit were included in this analysis. The number of days without recurrence was defined as the difference between the first day of treatment and either the date of recurrence, the date of loss to follow-up without clinical recurrence, or the date of the first dose of antibiotics for an intercurrent infection. Kaplan–Meier survival curves were constructed from these data for each treatment group.

#### Evaluation of bacteriologic efficacy

This analysis only took into account group A streptococci, the only organism clearly identified as pathogenic in pharyngitis. Patients eligible for this analysis were those evaluable for clinical efficacy, by protocol, at the end of treatment, who had group A streptococci cultured from their first sample. Samples received within 7 days by the central laboratory (initial sample and end-of-treatment sample) were taken into account, in order to describe the maximum number of streptococcal pharyngitis cases. Bacteriologic efficacy at the end of treatment was judged satisfactory if group A streptococci were eradicated, and otherwise as unsatisfactory.

#### Evaluation of tolerance

Tolerance was assessed from the data collected at the end of treatment on the basis of the number of patients who experienced one or more adverse events in each treatment group.

#### Evaluation of compliance

Compliance, judged by the number of tablets taken (recorded by the investigator), was considered good if

at least 80% of the treatment course had been taken (eight tablets of CPD or 24 tablets of PNV or AMC).

### Statistical analysis

The number of subjects necessary to show a difference of 10% between CPD and one of the other study drugs was 395 per treatment group, assuming a clinical success rate of 95% at the end of treatment, with a first-order risk of 2.5% and a second-order risk of 2.5% (instead of 5%, as there were three treatment groups).

The relapse rate at 6 months with the reference treatment was unknown. The power of comparisons involving recurrence rates based on survival curves was thus calculated retrospectively, and was 90% for the comparison of CPD with AMC, and 80% for the comparison of CPD with PNV.

Comparisons of frequencies were made using the chi-squared test or Fisher's exact test. In cases of an overall difference between the three groups, the CPD group was compared with each of the other two groups. The comparison of changes in qualitative parameters was based on the Mantel–Haenszel adjusted chi-squared test. Means were compared using one-way analysis of variance; in case of a significant overall difference, the groups were compared two-by-two using Dunnet's T test. Recurrences after successful treatment were analyzed by the Kaplan–Meier method. The three treatments were compared by means of the log-rank test, and then two-by-two when the difference was significant. In addition, a Cox model was used to identify variables with independent influence on the recurrence rate. The variables entered in the model were those recorded at enrollment and found to have significant influence in a univariate analysis.

## RESULTS

### Description of the population

Among the 580 patients randomized between March 1992 and June 1992, five were excluded from the analyses (four lost to follow-up, one took no treatment); 575 patients were thus evaluable for analysis of clinical tolerance. The evaluation of clinical efficacy at the end of treatment involved 513 patients, as 62 patients were excluded because of major deviations from the protocol. Among these 513 patients, 469 were evaluable for long-term outcome, while 44 were unevaluable; the outcome of treatment had been a clinical failure in 41 of them, and three had received another antibiotic at the end of treatment, based on the results of throat culture. In total, 389 patients were included in the assessment of clinical efficacy during follow-up, as 124 patients were unevaluable (44 patients excluded from the Kaplan–Meier analysis, 70 patients who had received an antibiotic for an intercurrent infection during the follow-up period, and 10 patients whose final visit had not taken place at M6 or M7).

Among the 575 patients evaluable for tolerance (205 men and 370 women; median age 33.7±12.6 years; mean body weight 64.1±13 kg), the demographic characteristics, medical history and presenting signs and symptoms were comparable in the three groups (Table 1). The analysis of the same parameters in the population eligible for the analysis of clinical efficacy also failed to show significant differences between the three groups.

### Clinical efficacy by protocol at the end of treatment

In the 513 patients evaluable for this analysis, the rate of satisfactory clinical responses was not significantly different between the three groups (Table 2). Among the patients in whom the clinical response was satisfactory, the mean time required for a subjective improvement was significantly shorter on CPD (2.5±0.8 days) than on PNV (3.3±1.3 days) and AMC (3.3±1.3 days) (global comparison, $p<0.001$). Similarly, the time required for a subjective cure was significantly shorter on CPD (4±1.3 days) than on PNV (5.4±1.9 days) and

**Table 1** Clinical and demographic characteristics of patients evaluable for tolerance

| | CPD ($n$=188) | PNV ($n$=187) | AMC ($n$=200) | $p$ |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age (years, $m$±SD) | 33.37±12.29 | 34.03±12.81 | 33.64±12.75 | NS |
| Weight (kg, $m$±SD) | 65.07±13.66 | 63.71±12.34 | 63.63±12.48 | NS |
| Sex (M/F) | 72/116 | 62/125 | 71/129 | NS |
| Medical history | | | | |
| Number of episodes in last 12 months ($m$±SD) | 4.26±1.22 | 4.25±1.30 | 4.21±1.18 | NS |
| Tonsillectomy (yes/no) | 16/172 | 20/167 | 26/174 | NS |
| Date of last pharyngitis (days, $m$±SD) | 70.07±43.89 | 71.58±47.26 | 73.86±47.38 | NS |
| Time from clinical onset (days, $m$±SD) | 2.05±3.81 | 1.89±2.47 | 1.90±2.26 | NS |

CPD=cefpodoxime proxetil; PNV=penicillin V; AMC=amoxycillin+clavulanic acid; NS=not significant; $m$=mean.

**Table 2** Analysis of clinical efficacy by protocol at the end of treatment

| Clinical response | CPD ($n$=170) | PNV ($n$=166) | AMC ($n$=177) |
|---|---|---|---|
| Satisfactory (%) * | 157 (92.35) | 147 (88.55) | 168 (94.92) |
| Unsatisfactory (%) | 13 (7.65) | 19 (11.45) | 9 (5.08) |

CPD=cefpodoxime proxetil; PNV=penicillin V; AMC=amoxycillin+clavulanic acid; *$p$=0.09.

AMC (5.6±2.2 days) (global comparison, $p<0.001$). This difference was also found in the Kaplan–Meier plots of subjective amelioration and cure among the patients who were evaluable at the end of treatment.

### Clinical efficacy by protocol at the end of follow-up

The results obtained in the 389 evaluable patients (Table 3) show that the rate of non-recurrence was significantly higher in the CPD group than in the PNV group ($p$=0.01) and AMC group ($p<0.01$). In contrast, no significant difference was found as regards the mean time to recurrence (Table 3).

### Clinical efficacy: Kaplan–Meier plots

Figure 1 shows the 'non-recurrence' curves in the three treatment groups. The three curves were globally different. Two-by-two comparisons (log-rank test) confirmed the absence of a significant difference between the PNV and AMC curves. In contrast, the CPD curve differed significantly from the PNV curve ($p$=0.01) and the AMC curve ($p<0.01$).

The influence of treatment on the onset of recurrences was studied by means of a Cox model, which confirmed that recurrences during follow-up were linked to the study drug, even after adjustment for baseline variables (type of treatment, sex, salaried job, age in two arbitrary classes (<40 years and ≥40 years), tonsillectomy, temperature at inclusion >38°C, and number of episodes of pharyngitis in the previous 12 months, also divided into two classes relative to the

**Table 3** Clinical efficacy at follow-up (month 6 or month 7): comparison of the recurrence rate according to treatment (per protocol analysis)

| | CPD ($n$=130) | PNV ($n$=122) | AMC ($n$=137) | $p$ |
|---|---|---|---|---|
| Success no. (%) | 108 (83.08) | 85 (69.67) | 94 (68.61) | <0.001 |
| Recurrence no. (%) | 22 (16.92) | 37 (30.33) | 43 (31.39) | |
| Time to recurrence (days, mean±SEM) | 84±50 | 84±49 | 78±41 | NS |

CPD=cefpodoxime proxetil; PNV=penicillin V; AMC=amoxycillin+clavulanic acid; NS=not significant.

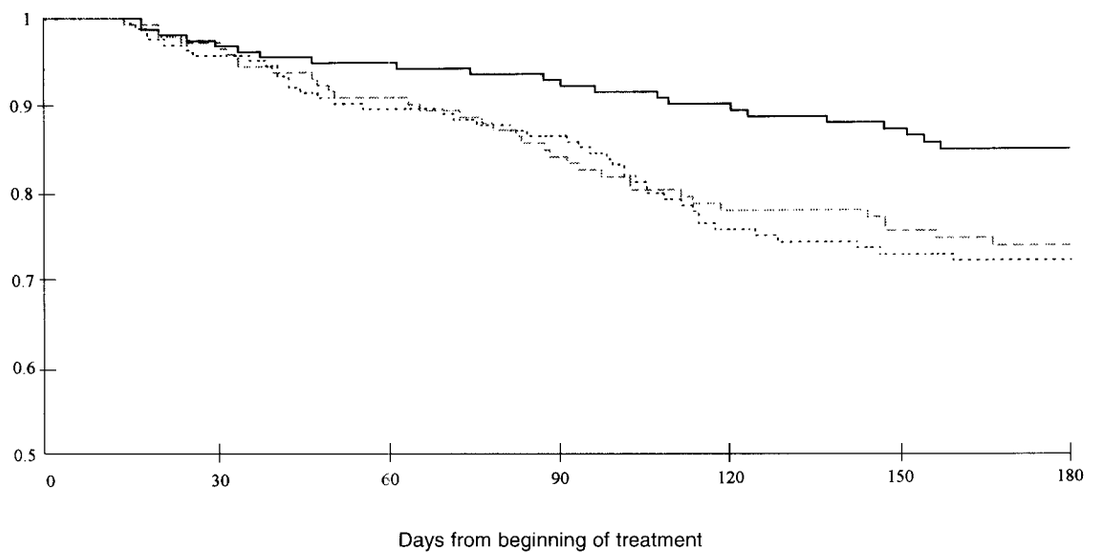


**Figure 1** Kaplan–Meier plots of non-recurrence in patients with satisfactory clinical results at the end of treatment. —— cefpdoxime proxetil ($n$=156); . . . . . penicillin V ($n$=147); – – – – amoxycillin-clavulanate ($n$=166).

median of episode number (<4 per year and ≥4 per year)).

The results of the Cox model used to identify parameters independently linked to recurrences showed that these were significantly less frequent after treatment with CPD than with PNV and AMC ($p<0.002$), less frequent in patients over 40 ($p<0.001$), and more frequent in patients who had had at least four previous episodes.

### Pathogens isolated at inclusion

The rapid diagnostic test for group A streptococci had a sensitivity of 73%, a specificity of 91%, a positive predictive value of 61% and a negative predictive value of 94.5% (Table 4).

Among the 575 patients evaluable for tolerance, 540 samples were received by the central laboratory and 385 were taken into account in the results because they were received within 3 days of sampling. According to the criteria described in the Patients and Methods section, strains were considered significant (i.e. probably pathogenic or copathogenic) in 185 (48%) samples, 23% of which yielded more than one potential pathogen. The nature and frequency of the isolates are given in Table 5.

**Table 4** Sensitivity of the GABHS rapid diagnostic test: results compared with those of culture in patients with an initial sample received within 3 days at the central laboratory

| | Culture | | |
|---|---|---|---|
| | Negative | Positive | Total |
| Rapid test not done | 0 | 2 | – |
| Negative rapid test | 291 | 17 | 308 |
| Positive rapid test | 29 | 46 | 75 |
| Total | 320 | 63 | 383 |

Sensitivity: 46/63=73.02%.
Specificity: 291/320=90.94%.
Positive predictive value: 46/75=61.33%.
Negative predictive value: 291/308=94.48%.

**Table 5** Pathogens cultured at inclusion (385 throat swabs)

| Pathogen | *n* (%) |
|---|---|
| GABHS | 65 (16.9) |
| GCBHS | 23 (6) |
| GGBHS | 8 (2.1) |
| *Haemophilus influenzae*[a] | 5 (1.3) |
| *Staphylococcus aureus*[a] | 22 (5.7) |
| Enterobacteriaceae[b] | 51 (13.2) |
| Non-fermenting Gram-negative bacilli[b] | 13 (3.4) |

GABHS=group A β-hemolytic streptococci; GCBHS=group C β-hemolytic streptococci; GGBHS=group G β-hemolytic streptococci.
[a]In samples without β-hemolytic streptococci, including one sample that contained both *Haemophilus influenzae* and *Staphylococcus aureus*.
[b]In the samples in which none of the above species were isolated, including a sample containing both a member of the Enterobacteriaceae and non-fermenting Gram-negative rods.

### Eradication of group A streptococci

Among the 59 patients evaluable for this parameter, bacteriologic efficacy was satisfactory (eradication of group A streptococci) in 96% (22/23) cases on CPD, 100% (16/16) on PNV and 95% (19/20) on AMC (statistically not significant). The two bacteriologic failures (one patient on CPD and one on AMC) were clinical successes at the end-of-treatment assessment.

### Tolerance

Among the 575 patients evaluable for tolerance, 64 experienced at least one side effect. The number of patients who experienced at least one side effect was lower in the CPD group (2/188 patients: 1%) than in the PNV group (16/187 patients: 8.6%) or the AMC group (46/200 patients: 23%). These differences were significant ($p<0.001$ for CPD versus AMC, and CPD versus PNV). Side effects were mainly of a gastrointestinal nature, and occurred in two patients on CPD, nine patients on PNV and 42 patients on AMC. Side effects necessitated treatment withdrawal in 13 cases (seven patients in the PNV group, six in the AMC group, and none in the CPD group).

### Compliance

Among the 566 cases in which the number of tablets effectively taken was noted, 17 (9%) of the 183 patients on PNV and 16 (8%) of the 196 patients on AMC were considered as showing poor compliance (less than 80% of the planned tablets). In contrast, this occurred in none of the 187 patients on CPD. The difference between the CPD group and the other two groups was significant ($p<0.001$ for both comparisons).

## DISCUSSION

The optimal treatment of acute pharyngitis is a matter of debate in several countries. The main preoccupation is to eradicate group A streptococci, in order to prevent acute rheumatic fever. Other considerations are cost and the impact of antibiotics on the microbial ecology. In France, GABHS rapid screening tests are not available for reasons inherent in the public healthcare system. The recommendation is thus to treat all acute episodes of pharyngitis with antibiotics, regardless of the age of the patient, a 10-day course of PNV remaining the reference treatment. For French authorities,

β-lactam agents combined with β-lactamase inhibitors, and β-lactamase-resistant cephalosporins should be reserved for recurrent pharyngitis. On the other hand, a number of shorter treatment courses have been proposed; however, they have been exclusively assessed in patients with acute streptococcal pharyngitis [15–19, 22–25].

This is the first trial of a 5-day treatment with CPD at a dose of 100 mg morning and evening for recurrent pharyngitis irrespective of bacterial etiology. In order to conduct a study with nationwide relevance, and to assess the value of the routine use of the GABHS rapid test, we chose to select as investigators a large number of general practitioners scattered throughout the French territory, who were asked to recruit three patients each. A 73% sensitivity of the GABHS rapid test was demonstrated in this setting. This study had an open design, so that a cost-effectiveness study could be conducted in parallel, and the compliance to regimens with different daily doses and different durations could be assessed. To minimize judgment biases, all the files were blindly reviewed by the study coordinator.

Our results, obtained in a large population, show that 5 days of treatment with CPD is as effective, in clinical terms, as a 10-day course of AMC or PNV in the treatment of the initial acute symptoms. In addition, the 5-day CPD schedule was associated in this trial with a better compliance and a better clinical tolerance relative to the comparators. Although group A streptococci eradication rates were similar in the three treatment arms, definite conclusions about this secondary criterion cannot be drawn because of the small size of the population concerned. Unexpectedly, a significant fall in the rate of recurrent episodes occurring during the 6-month follow-up period was observed in the CPD group as compared to the PNV and AMC groups, with a high power of comparisons based on survival curves.

Neither identification of viral agents nor bacteriologic studies of the recurrent episodes were planned in our analysis. However, we were able to establish that the bacteria isolated at the time of inclusion did not correlate with recurrence in any of the three treatment groups. It should be noted that, besides treatment itself, additional factors interfering with the outcome are an age <40 and a frequency of episodes of pharyngitis >4 per year.

In these adult patients with a history of at least three clinical episodes of pharyngitis per year, the decrease in recurrence rate observed following a 5-day course of CPD is an interesting result which requires further confirmation and whose mechanism deserves further investigation. In addition, this 5-day treatment study reinforces the previous results in trials of 5-day courses of CPD in the treatment of streptococcal pharyngitis.

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**References**

1. Conférence de Consensus organisée par l'AFORCOPI (Association pour la Formation Continue en Pathologie Infectieuse). Le traitement des angines aiguës et la prevention de leurs complications. Med Mal Infect 1991; 21: 277–84.
2. Brook I, Yocum P, Shah K. Surface vs core tonsillar aerobic and anaerobic flora in recurrent tonsillitis. JAMA 1980; 244: 1696–8.
3. Brook I, Foote PA. Comparison of the microbiology of recurrent tonsillitis between children and adults. Laryngoscope 1986; 96: 1385–8.
4. Brook I. Treatment of patients with acute recurrent tonsillitis due to group A β-haemolytic streptococci: a prospective randomized study comparing penicillin and amoxycillin/clavulanate potassium. J Antimicrob Chemother 1989; 24: 227–33.
5. Portier H, Chavanet P, Ichou F, Le Groupe Multicentrique. Profil bactériologique de l'angine de l'adulte. Absence d'influence du caractère récidivant [abstract 243/P15]. 10th Réunion Interdisciplinaire de Chimiotherapie Anti-Infectieuse, Paris, 1990.
6. Kielmovitch IH, Keleti G, Bluestone CD, Wald ER, Gonzalez C. Microbiology of obstructive tonsillar hypertrophy and recurrent tonsillitis. Arch Otolaryngol Head Neck Surg 1989; 115: 721–4.
7. Agren K, Lundberg C, Nord CE. Effect of amoxycillin/clavulanic acid on the aerobic and anaerobic tonsillar microflora in the treatment of recurrent tonsillitis. Scand J Infect Dis 1990; 22: 691–7.
8. Timon CI, McAllister VA, Walsh M, Cafferkey MT. Changes in tonsillar bacteriology of recurrent acute tonsillitis: 1980 vs. 1989. Respir Med 1990; 84: 395–400.
9. Stafford N, von Haacke N, Sene A, Croft C. The treatment of recurrent tonsillitis in adults. J Laryngol Otol 1986; 100: 175–7.
10. Stjernquist-Desatnik A, Prellner K, Schalén C. Colonization by Haemophilus influenzae and group A streptococci in recurrent acute tonsillitis and in tonsillar hypertrophy. Acta Otolaryngol 1990; 109: 314–19.
11. Rosen G, Samuel J, Vered I. Surface tonsillar microflora versus deep tonsillar microflora in recurrent acute tonsillitis. J Laryngol Otol 1977; 91: 911–13.
12. Bieluch VM, Chasin WD, Martin ET, Tally FP. Recurrent tonsillitis: histologic and bacteriologic evaluation. Ann Otol Rhinol Laryngol 1989; 98: 332–5.
13. Brook I. Role of beta-lactamase-producing bacteria in the failure of penicillin to eradicate Group A streptococci. Pediatr Infect Dis 1985; 4: 491–5.

14. Brown RJ, Batts DH, Hughes GS, Greenwald CA, the Cefpodoxime Pharyngitis Study Group. Comparison of oral cefpodoxime proxetil and penicillin V potassium in the treatment of Group A streptococcal pharyngitis/tonsillitis. Clin Ther 1991; 13: 579–88.
15. Portier H, Chavanet P, Waldner-Combernoux A, et al. Five versus ten days treatment of streptococcal pharyngotonsillitis: a randomized controlled trial comparing cefpodoxime proxetil and phenoxymethyl penicillin. Scand J Infect Dis 1994; 26: 59–66.
16. Dajani AS, Kessler SL, Mendelson R, Uden DL, Todd WM. Cefpodoxime proxetil vs. penicillin V in pediatric streptococcal pharyngitis/tonsillitis. Pediatr Infect Dis J 1993; 12: 275–279.
17. Portier H, Zuck P, Voiriot P, Stahl JP, Lucht F, Clermont A. Cefpodoxime proxetil 5 days versus penicillin V 10 days in adult patients with GABHS pharyngitis: evaluation of efficacy and safety. [abstract 1321]. In: 18th International Congress of Chemotherapy, Stockholm, 1993.
18. Pichichero ME, Gooch WM, Rodriguez W, et al. Effective short-course treatment of acute group A β-hemolytic streptococcal tonsillopharyngitis. Ten days of penicillin V vs 5 days or 10 days of cefpodoxime therapy in children. Arch Pediatr Adol Med 1994; 148: 1053–60.
19. Dajani A, Sheaffer C, Andresen J, Denny F. Short-course treatment of group A streptococcal (GAS) pharyngitis. Clin Infect Dis 1994; 19: 594.
20. Portier H, Chavanet P, Cohen R, et al. Five days cefpodoxime proxetil (RU 51807) vs 10 days penicillin V for streptococcal pharyngitis/tonsillitis in children [abstract 1674]. In: Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, 1994.
21. Pelc A, Portier H, Gehanno P, Fiessinger S, Ichou F. Cost saving of 5-day therapy with cefpodoxime proxetil versus standard 10-day β-lactam therapy for recurrent pharyngotonsillitis in adults. A prospective general practice study. PharmacoEconomics 1996; 10(3): 239–50.
22. Géhanno P, Chiche D. Traitement des angines à streptocoque bêta-hémolytique du groupe A par le céfuroxime axetil pendant 4 jours: étude comparative à la pénicilline V pendant 10 jours. Med Mal Infect 1991; 21(suppl): 66–70.
23. Peyramond D, Tigaud S, Darchy L, Bremard-Oury C, Le Groupe de Travail. Etude multicentrique comparant l'efficacité du céfixime pendant 4 jours à la phénoxyméthylpénicilline pendant 10 jours chez des patients ayant une angine à streptocoque bêta-hémolytique du groupe A. Med Mal Infect 1993; 23(suppl): 419–26.
24. Carbon C, Chatelin A, Bingen E, et al. A double-blind randomized trial comparing the efficacy and safety of a 5-day course of cefotixam hexetil with that of a 10-day course of penicillin V in adult patients with pharyngitis caused by group A β-haemolytic streptococci. J Antimicrob Chemother 1995; 35(6): 843–54.
25. Aujard Y, Boucot I, Brahimi N, Chiche D, Bingen E. Comparative efficacy and safety of four-day cefuroxime axetil and ten-day penicillin treatment of group A beta-hemolytic streptococcal pharyngitis in children. Pediatr Infect Dis J 1995; 14: 295–300.